

ORIGINAL ARTICLE

Dry night cough as a marker of allergy in preschool children: the PARIS birth cohort

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Abstract

Background: Early detection of children at risk for developing allergy is an important challenge. Our first analyses in infants from the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort suggested that dry night cough was associated with parental-reported allergic disorders. The aim of the present study was to refine this finding by investigating the time course of dry night cough from birth to age 4 yr in relation to blood markers of atopy and allergic morbidity.

Methods: Health outcomes were regularly assessed by parental self-administered questionnaires. Blood markers of atopy were measured at age 18 months. Children with similar patterns of dry night cough over the first 4 yr of life were grouped together using *k*-means clustering. Associations with atopy/allergy were studied using multinomial logistic regression.

Results: Three trajectories of dry night cough were identified in 1869 children. Besides the never/infrequent pattern (72.4%), the transient pattern (8.8%) was composed of children who coughed in the first year and recovered by age 4 yr, while the rising pattern (18.8%) included all symptomatic children at age 4 yr, whether they were persistent or late coughers. Compared with the never/infrequent pattern, the rising pattern was significantly associated with elevated total immunoglobulin E (IgE) level (odds ratio [OR] = 1.70, 95% confidence interval [CI] = 1.21–2.39) and inhalant allergens sensitization (OR = 2.66, 95% CI = 1.26–5.61) at age 18 months, and with doctor-diagnosed allergic diseases over the first 4 yr such as hay fever (OR = 2.52, 95% CI = 1.49–4.26) and eczema (OR = 1.29, 95% CI = 1.00–1.66).

Conclusions: This study provides evidence that persistent/late dry night cough may indicate allergy in preschool children.

Early detection of children at risk for developing allergic asthma is challenging because most of those who suffer from respiratory manifestations in infancy will not develop the disease in later life. Among the common respiratory disorders that may affect children, cough is a symptom of growing interest because of the large number of outpatient consultations and over-the-counter drug uses for which it is responsible (1). Due to its non-specific nature, the differential diagnosis is wide, and several guidelines have been recently published on this topic (2–4). In preschoolers, cough may indicate asthma, especially when occurring at night and without respiratory infection (5). However, cough has so far received less attention than wheezing in epidemiological studies on early asthma.

As part of the Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort, our first analyses suggested that toddlers

who experienced dry night cough were more likely to be associated with allergic features as reported by parents (6, 7). As we hypothesized that all preschool coughers may not represent a single phenotype, the aim of the present study was to investigate the time course of dry night cough in PARIS children by identifying symptom trajectories in the first 4 yr of life and to examine their relations with blood markers of atopy and allergic morbidity.

Methods

Population and study design

The PARIS birth cohort enrolled full-term healthy babies born between 2003 and 2006 in five Paris maternity hospitals.

Details about enrollment criteria are provided elsewhere (8). Among the 4177 mothers who agreed to take part in the study, 337 did not return any mailed questionnaires, resulting in a final cohort of 3840 infants. The study protocol was approved by the French Ethical Committee, and written informed consent was obtained from the parents.

In this study, we considered data collected from birth to age 4 yr including a mother's interview at birth, annual self-administered questionnaires, and a health examination at age 18 months.

Health outcomes

Health outcomes were mostly assessed by core questions from the International Study of Asthma and Allergies in Childhood (9). At 1, 2, 3 and 4 yr of age, parents were questioned about the occurrence in the previous year of dry night cough apart from a respiratory infection. Parents also reported whether their child experienced wheezing, nose, or skin disorders. At age 4 yr, the following outcomes were defined:

- 1 Wheezing: at least one episode of wheezing in the chest in the previous year
- 2 Rhinoconjunctivitis-like symptoms: sneezing or runny/nose apart from a cold associated with itchy-watery eyes in the previous year
- 3 Atopic dermatitis-like symptoms: itchy rash coming and going for at least 6 months, affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck/ears/eyes in the previous year

Lastly, whether a doctor had ever diagnosed the child with asthma, eczema, hay fever or food allergy was documented at each birthday.

Biological data

At age 18 months, 2012 infants attended a health examination offered to all PARIS children, this including a blood sample. Serum was analyzed for total/specific immunoglobulin E (IgE) and eosinophil count. Elevated total IgE level was defined as a concentration of 45 IU/ml or greater, and eosinophilia as a concentration of 470 eosinophils/ μ l or greater (10). Sensitization against a mixture of common inhalant and food allergens was assessed with a multi-allergen-specific IgE screen using ImmunoCAP Phadiatop[®] and Trophatop[®] fx26/fx27/fx28 (Phadia, Uppsala, Sweden). The detection limit was set at 0.35 IU/ml.

Familial and environmental factors

At the maternity hospital, the mother was interviewed about family characteristics, notably related to parental history of allergy, smoking habits during pregnancy, presence of older siblings, and parental occupation. Familial socioeconomic status (SES) was determined according to the highest position among the two parents, and divided into three categories (low, medium, and high).

Children's exposure to passive smoking in the home was documented at 1 month of age by a phone interview of the

mother or father, and then by self-administered questionnaires mailed to the parents at 3, 6, 9, 12, 18, 24, 36, and 48 months of age.

Statistical analysis

Clustering was used to identify patterns of dry night cough in the study population with a *k*-means algorithm designed for longitudinal data (11). Children were partitioned into different trajectory groups according to the occurrence of dry night cough in the first, second, third, and fourth years of life. The analysis was carried out on children with complete report of cough at all four time points. Briefly, each child was first assigned to a cluster at random. The algorithm was then iterated several times so that children in the same cluster had the closest Euclidean distance from one another, while children in different clusters were as far as possible. Repeated run were performed to reach the model with the best data separation according to the Davies-Bouldin index (12).

The general characteristics of children from the identified trajectories of dry night cough were compared using chi-squared test. The associations of trajectory membership with blood markers of atopy, allergic symptoms, and doctor-diagnosed diseases were then studied using multinomial logistic regression. Results were expressed as odds ratios (OR) and their 95% confidence intervals (95% CI).

Cluster analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Regression analyses were fitted using Stata/SE 9.1 software (StataCorp, College Station, TX, USA).

Results

Study population

The questionnaire relating to the child's health at age 4 yr was filled in for 2042 children, that is, 53% of the original cohort. Among the 1798 children for whom this questionnaire was not completed, 533 (i.e., nearly 30%) had to stop the follow-up before their fourth birthday due to moving outside the study area, a withdrawal criterion specified in the protocol (8).

When comparing the baseline characteristics of children followed and not followed at age 4 yr, no significant difference was found except for familial SES, maternal age: children who were still participating at age 4 yr were more likely to have a higher familial SES and an older mother than children of the initial cohort no longer participating at age 4 yr.

Prevalence and trajectories of dry night cough

The annual prevalence of dry night cough was, respectively, 14.1%, 14.3%, 16.5%, and 18.8% during the first, second, third, and fourth years of life. Nearly four in ten children experienced such episodes between birth and age 4 yr.

Three patterns of dry night cough were identified in 1869 children with complete information about cough at all time points (Fig. 1). Children from the never/infrequent pattern were all asymptomatic at 1 and 4 yr, and a few of them had

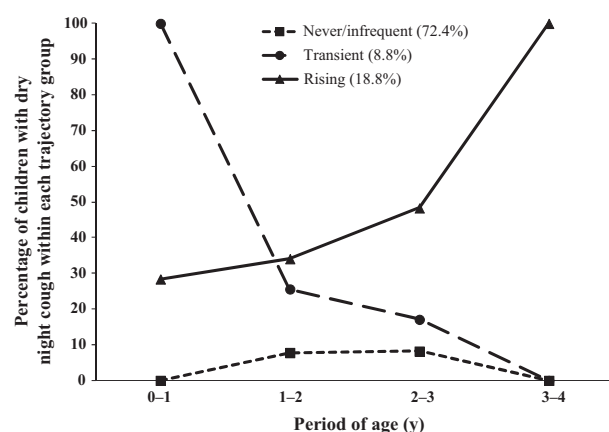


Figure 1 Trajectories of dry night cough identified during the first 4 yr of life in the PARIS birth cohort by *k*-means cluster analysis (*n* = 1869).

cough during their second or third year (7.8% and 8.2%, respectively). The transient pattern consisted of coughers at age 1 yr who had recovered when aged 4 yr. In the rising pattern, the prevalence of cough increased throughout the first 4 yr of

life, and all children from this group experienced cough by 4 yr of age. This rising pattern could be split into two subgroups depending on the age at the first onset of cough. While late coughers (*n* = 181, 51.4%) started to cough when aged 3 or 4 yr, persistent coughers (*n* = 171, 48.6%) started to cough before 2 yr of age and were still symptomatic when aged 4 yr.

The general characteristics of children from these three patterns of cough are listed and compared in Table 1. A significant difference was shown for parental history of allergy and prenatal exposure to smoking, with a higher proportion of children with parental allergy in the rising pattern, and a higher proportion of children whose mother smoked during pregnancy in the transient pattern.

Relation between dry night cough and allergy

The never/infrequent pattern was considered as the reference group in all analyses. Table 2 describes the relations between dry night cough patterns and allergic features in terms of medical diagnoses and clinical symptoms. Children from the rising pattern were more likely to be diagnosed with asthma, eczema, hay fever and food allergy during their first 4 yr of life, and reported significantly more often current symptoms of wheezing, rhinoconjunctivitis, and atopic dermatitis by

Table 1 General characteristics of children from the dry night cough patterns identified during the first 4 yr of life in the PARIS birth cohort

	Overall (N = 1869)	Dry night cough patterns			p*
		Never/infrequent (n = 1353)	Transient (n = 164)	Rising (n = 352)	
Gender					
Male	950 (50.8)	670 (49.5)	88 (53.7)	192 (54.5)	0.183
Female	919 (49.2)	683 (50.5)	76 (46.3)	160 (45.5)	
Familial SES [†]					
Low	109 (5.8)	74 (5.5)	11 (6.7)	24 (6.8)	0.487
Medium	486 (26.0)	342 (25.3)	49 (29.9)	95 (27.0)	
High	1274 (68.2)	937 (69.2)	104 (63.4)	233 (66.2)	
Parental history of allergy [‡]					
No	859 (46.2)	646 (48.0)	72 (43.9)	141 (40.3)	0.001
Yes, one parent	793 (42.6)	567 (42.1)	77 (47.0)	149 (42.6)	
Yes, both parents	209 (11.2)	134 (9.9)	15 (9.1)	60 (17.1)	
Maternal age at birth					
<35 yr	1355 (72.5)	960 (71.0)	119 (72.6)	276 (78.4)	0.020
≥ 35 yr	514 (27.5)	393 (29.0)	45 (27.4)	76 (21.6)	
Older siblings					
No	1051 (56.2)	746 (55.1)	98 (59.8)	207 (58.8)	0.296
≥ 1	818 (43.8)	607 (44.9)	66 (40.2)	145 (41.2)	
Prenatal exposure to ETS [§]					
No	1687 (90.3)	1232 (91.1)	139 (84.8)	316 (89.8)	0.035
Yes	182 (9.7)	121 (8.9)	25 (15.2)	36 (10.2)	
Postnatal exposure to ETS [¶]					
No	1246 (68.0)	923 (69.4)	99 (62.7)	224 (65.1)	0.101
Yes	586 (32.0)	407 (30.6)	59 (37.3)	120 (34.9)	

ETS, environmental tobacco smoke; SES, socioeconomic status. *Comparison of children from the 3 patterns of dry night cough using chi-squared test. †Low: low-level white-collar workers, blue-collar workers and unemployed; medium: intermediate-level white-collar workers, craftsmen and shopkeepers; high: high-level white-collar workers. ‡Among asthma, eczema, and/or allergic rhinitis. §Maternal active smoking during pregnancy. ¶Presence of a regular smoker (smoking every day) in the home during the first 4 yr of life. All data are presented as *n* (%).

Table 2 Associations of the dry night cough patterns identified during the first 4 yr of life in the PARIS birth cohort with respiratory/allergic morbidity at age 4 yr

	Dry night cough patterns							
	Never/infrequent pattern	Transient pattern			Rising pattern			
		%	%	OR (95% CI)*	p	%	OR (95% CI)*	p
Model 1: Diseases ever doctor-diagnosed at age 4 yr								
Asthma	7.2	20.4	3.27 (2.11–5.08)	<0.001	26.2	3.93 (2.84–5.43)	<0.001	
Eczema	36.7	42.6	1.20 (0.85–1.69)	0.296	47.9	1.29 (1.00–1.66)	0.052	
Hay fever	2.7	1.9	0.54 (0.16–1.80)	0.318	9.1	2.52 (1.49–4.26)	0.001	
Food allergy	8.2	9.9	1.03 (0.58–1.83)	0.909	16.8	1.63 (1.12–2.36)	0.010	
Model 2: Current symptoms at age 4 yr								
Wheezing	3.5	8.3	2.54 (1.34–4.83)	0.004	16.0	4.56 (2.98–6.99)	<0.001	
Rhinoconjunctivitis-like symptoms	2.6	2.6	0.91 (0.32–2.63)	0.869	11.3	3.60 (2.18–5.94)	<0.001	
Atopic dermatitis-like symptoms	10.7	10.2	0.92 (0.53–1.60)	0.779	20.9	1.85 (1.33–2.58)	<0.001	

CI, confidence interval; OR, odds ratio. *Multinomial logistic regression model (outcome: never/infrequent pattern, transient pattern, rising pattern). The reference group is the never/infrequent pattern of dry night cough. Each model included all the variables listed.

4 yr of age. No associations were found for the transient pattern except for doctor-diagnosed asthma and wheezing symptoms.

Associations between dry night cough patterns and blood markers of atopy at age 18 months are shown in Table 3. The rising pattern was positively associated with elevated total IgE level and atopic sensitization to common inhalant and food allergens. Compared to children from the never/infrequent pattern, children from the rising pattern were about 2.5 times more likely to be sensitized to inhalant allergens when aged 18 months. Contrarily, the transient pattern was not associated with any biomarkers of atopy.

Lastly, it is interesting to notice that most of the relations between the rising pattern and atopy/allergy outcomes persisted whether cough was isolated or associated with wheeze in the fourth year and whether children were late or persistent coughers (Table 4).

Discussion

This study highlighted three trajectories of dry night cough among preschoolers in a population-based birth cohort. Besides children who infrequently or transiently suffered from cough, we identified a group consisting of late coughers (starting to cough after age 2 yr) and persistent coughers (starting to cough before age 2 yr and still coughing at age 4 yr), which was clearly associated with atopy and allergic morbidity, whether cough was isolated or associated with wheeze.

Strengths and limitations

One strength of this study is its prospective design from birth, which enabled us to investigate the natural course of cough during the preschool years, a critical time in life due to the lung

Table 3 Associations of the dry night cough patterns identified during the first 4 yr of life in the PARIS birth cohort with blood markers of atopy at age 18 months

	Dry night cough patterns							
	Never/infrequent pattern	Transient pattern			Rising pattern			
		%	%	OR (95% CI)*	p	%	OR (95% CI)*	p
Blood markers of atopy								
Elevated total IgE (≥45 IU/ml)	19.4	17.8	0.90 (0.53–1.55)	0.710	29.0	1.70 (1.21–2.39)	0.002	
Eosinophilia (≥470 eosinophils/μl)	12.2	10.0	0.80 (0.41–1.59)	0.532	15.4	1.32 (0.86–2.02)	0.201	
Sensitization to common inhalant allergens	2.2	2.0	0.91 (0.21–4.00)	0.904	5.6	2.66 (1.26–5.61)	0.010	
Sensitization to common food allergens	13.5	10.1	0.72 (0.36–1.43)	0.351	22.1	1.83 (1.25–2.66)	0.002	
Sensitization to any common allergens	14.6	10.1	0.66 (0.33–1.30)	0.228	25.0	1.95 (1.36–2.81)	<0.001	

CI, confidence interval; IgE, immunoglobulin E; IU, international unit; OR, odds ratio. *Multinomial logistic regression model (outcome: never/infrequent pattern, transient pattern, rising pattern). The reference group is the never/infrequent pattern of dry night cough. Each blood marker of atopy was included into a distinct model. Among the 1869 children included in the cluster analysis, at least one blood marker of atopy was measured in 1192 children at age 18 months (868 in the never/infrequent pattern, 102 in the transient pattern and 222 in the rising pattern).

Table 4 Associations of the rising pattern of dry night cough identified during the first 4 yr of life in the PARIS birth cohort with allergic morbidity and atopy, depending on whether children had wheezing or not at age 4 yr, and whether children were late or persistent coughers

	Rising pattern of dry night cough							
	No wheeze at 3–4 yr (n = 296)		Wheeze at 3–4 yr (n = 56)		Late coughers (n = 181)*		Persistent coughers (n = 171)*	
	OR (95% CI)†	p	OR (95% CI)†	p	OR (95% CI)‡	p	OR (95% CI)‡	p
Diseases ever doctor-diagnosed at age 4 yr								
Asthma	2.33 (1.60–3.39)	<0.001	29.61 (15.59–56.25)	<0.001	4.07 (2.72–6.07)	<0.001	3.74 (2.48–5.66)	<0.001
Eczema	1.32 (1.01–1.72)	0.039	1.04 (0.56–1.93)	0.911	1.25 (0.90–1.73)	0.192	1.32 (0.94–1.86)	0.108
Hay fever	2.31 (1.31–4.05)	0.004	3.67 (1.52–8.87)	0.004	2.19 (1.12–4.28)	0.021	2.87 (1.54–5.36)	0.001
Food allergy	1.59 (1.07–2.36)	0.021	1.87 (0.88–3.99)	0.106	1.32 (0.80–2.17)	0.276	1.96 (1.24–3.10)	0.004
Blood markers of atopy at age 18 months								
Elevated total IgE (≥ 45 IU/ml)	1.65 (1.15–2.38)	0.007	1.99 (0.95–4.17)	0.067	1.66 (1.06–2.60)	0.028	1.75 (1.12–2.74)	0.014
Eosinophilia (≥ 470 eosinophils/ μ l)	1.34 (0.85–2.11)	0.204	1.21 (0.46–3.18)	0.705	1.18 (0.66–2.11)	0.580	1.46 (0.85–2.53)	0.173
Sensitization to common inhalant allergens	2.38 (1.05–5.39)	0.037	4.11 (1.15–14.65)	0.029	1.74 (0.58–5.24)	0.325	3.62 (1.53–8.54)	0.003
Sensitization to common food allergens	1.88 (1.26–2.81)	0.002	1.55 (0.66–3.63)	0.310	2.14 (1.33–3.46)	0.002	1.53 (0.92–2.57)	0.104
Sensitization to any common allergens	1.95 (1.32–2.88)	0.001	1.95 (0.89–4.25)	0.093	2.05 (1.28–3.28)	0.003	1.85 (1.15–3.00)	0.012

CI, confidence interval; IgE, immunoglobulin E; IU, international unit; OR, odds ratio. *Late coughers started to cough when aged 3 or 4 yr, whereas persistent coughers started to cough before age 2 yr and were still symptomatic when aged 4 yr. †Multinomial logistic regression (outcome: never/infrequent pattern, rising pattern without wheeze, rising pattern with wheeze). The reference group is the never/infrequent pattern of dry night cough. ‡Multinomial logistic regression (outcome: never/infrequent pattern, late coughers from the rising pattern, persistent coughers from the rising pattern). The reference group is the never/infrequent pattern of dry night cough. All medical diagnoses were included into the same model, whereas each blood marker of atopy was included into a distinct model.

and immune system development. Recently, many studies utilized statistical methods to derive childhood respiratory/allergic phenotypes directly from the observed data without a priori assumptions (13). Some of these studies were cross-sectional and characterized groups of children only at a particular age (14, 15), whereas others were longitudinal cohort studies dealing with changes in symptomatology over the first years of life. This latter approach appears as the most relevant to improve the understanding of the development of atopic diseases in early childhood and has already been used to define trajectories of wheeze (16–18). Our study is innovative because, to the best of our knowledge, this is the first one to investigate trajectories of cough using a statistical approach. Lastly, this study includes the objective assessment of atopy at age 18 months. Only a few European birth cohort studies have measured serum IgE levels so early in life and in such a large sample of children (19). These data are particularly relevant because allergenic sensitization in infancy is a risk factor for developing atopic diseases including asthma at school age (20). It would also have been valuable to have biomarkers of atopy at age 4 yr, but blood samples were not collected at this time point in the PARIS cohort. Nevertheless, even though the prevalence of aeroallergens sensitization is still low at age

18 months, it is interesting to note that a significant difference between cough trajectories was detected.

One limitation encountered by this study is participation. The substantial attrition rate of the PARIS cohort has been previously discussed (7). Briefly, the study area encompasses the French capital city and its close suburb, which have one of the highest residential mobility rates in the country. Young people commonly first start their occupational life there, then move after starting a family. This is what we actually observed in our cohort, where about 30% of the children not followed at age 4 yr had to leave the study before their fourth birthday due to moving in other French regions or abroad. However, the comparison of children followed and not followed did not reveal any major difference except for the familial SES, which was significantly lower in children lost to follow-up, as generally encountered in other studies (16, 21). Lastly, another limitation could be that cough symptoms were reported by parents, like in many other large epidemiological studies in children (22, 23). Nevertheless, data were collected using an international standardized questionnaire (9), and the observed prevalences were consistent with the literature as mentioned below. The validity of this variable can, however, be questioned, particularly with regard to nocturnal occurrence. The

study by Fuller et al. (24) provides some answers: the authors compared parental reports of nocturnal cough with audio/video recordings and found that parents were reliable reporters. In our study, we may assume that parents were aware whether their child has coughed at night during the previous year as families of the PARIS cohort live in rather small apartments (mean surface area = 70 m²).

Dry night cough in relation with allergy

As previously described in other studies in the general population, cough apart from respiratory infections is a frequent symptom in childhood. In our study, the proportion of children with dry night cough over the 0–4 yr period was high (nearly 40%) and the annual prevalences between 1 and 4 yr were in accordance with the literature (22).

Our analyses revealed that preschoolers with dry night cough could be separated into two symptomatic patterns: transient and late/persistent coughers. The existence of different phenotypes of childhood cough had previously been suggested by Spycher et al. (25) who identified, among a sample of symptomatic children, two groups of coughers (transient and persistent) using latent class analysis. Compared with asymptomatics, the persistent cough phenotype was associated with reduced lung function, increased bronchial responsiveness and had a significantly higher risk of later wheeze, but no difference was found for the transient cough phenotype, suggesting separate conditions. This study did, however, include children with a wide age range, thus limiting comparison with our own results.

It is clearly established in preschoolers that wheezing alone is not enough to predict subsequent asthma, and evaluating young children with respiratory manifestations is a complex issue for clinicians. Our findings suggest that dry night cough may precisely help to distinguish those more likely to develop allergy in later life, given the associations found between the rising pattern and biomarkers of atopy, whether cough was associated to wheeze or not.

In the literature, the relation between childhood cough and asthma/allergy is still debated (26). Many studies have concluded that coughers do not differ from asymptomatic children with respect to atopic status, but the health outcome of interest was often cough apart from wheeze or other respiratory symptom (sometimes called 'isolated cough' or 'cough alone') (25, 27–31). Some authors have looked at cough irrespective of other respiratory symptoms, like Caudri

et al. (21) who found no significant association between night cough before age 4 yr and asthma at 7–8 yr. However, the latter authors considered the occurrence of at least one episode of cough during the 0–4 yr period and did not identify subgroups of coughers as in our study, which may explain the absence of association. The study by Dodge et al. (32) who considered the occurrence of cough at different time periods between 0 and 4 yr of age is more similar to ours. While cough during the first, second, and third years of life was not associated with subsequent asthma, chronic cough during the fourth year was a strong predictor of being diagnosed with asthma between 5 and 11 yr of age, with a risk 5.4 times that of children with no cough. Our findings are in accordance with this study, which suggested that all preschool coughers are not at equal risk for developing asthma and that only children with cough beginning or persisting in the fourth year are more likely to be subsequently diagnosed with the disease.

In conclusion, our analysis of the natural history of dry night cough during the preschool years distinguished a group of late/persistent coughers by age 4 yr more likely to be associated with atopic features. This suggests that symptom of dry night cough, even in absence of wheeze, could be helpful in the early detection of children prone to the subsequent development of allergic diseases.

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